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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 07/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/822,205	ZHAO ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *20 and 22-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Requirement to comply with sequence rules

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 because the specification recites on pages 42-43 sequences lacking sequence identifiers. The specification has not been exhaustively searched for instances of non-compliance. It is recommended that the entire specification be reviewed to ensure it fully complies with all sequence rules.

In order to be considered fully responsive any reply to this action must correct these deficiencies, as this requirement will not be held in abeyance.

Election/Restrictions

Applicant's election with traverse of invention I, claims 1-19 and 21, SEQ ID NO: 1 and the species corresponding to the first illustrated in claims 11 and 12, in the reply filed on January 27, 2006 is acknowledged. The traversal is on the ground(s) that formulae I and (v) have common structures such as X_1 and L_2. Applicant further argues that because the two inventions are identically classified the search of the two inventions will completely overlap. Applicant further argues that it would not be an undue burden to search inventions I and II at the same time. This is not found persuasive because while the formulae might share some common elements the search

of these two formulae would not be coextensive. While inventions I and II may share a classification, classified patent searches are not the only type of search performed during examination. Applicant traverses the restriction to a single nucleotide sequence by arguing that SEQ ID NOS: 2, 3 and 4 share substantial nucleotide overlap with the elected sequence. Because SEQ ID NOS: 2 and 4 differ from SEQ ID NO: 1 at only two positions, a search of SEQ ID NO: 1 will be adequate to also search SEQ ID NOS: 2 and 4. Therefore, applicant's arguments with regard to SEQ ID NOS: 2 and 4 are persuasive and these sequences are rejoined with SEQ ID NO: 1. Applicant's argument that SEQ ID NO: 3 shares 12 nucleotides with SEQ ID NO: 1 is not persuasive because with this degree of identity a search of SEQ ID NO: 1 is not sufficient to fully search SEQ ID NO: 3 and this sequence is not rejoined.

The requirement is still deemed proper and is therefore made FINAL.

Claims 20 and 22-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on January 27, 2006.

Claim Objections

Claim 3 is objected to because of the following informalities: this claim is ungrammatical because the word "is" in line 1 is unnecessary. Appropriate correction is required.

Claim 8 is objected to for the presence of non-elected subject matter, specifically SEQ ID NO: 3.

Claims 9 and 10 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 9 broadens rather than limits claim 1, in which R_1 and R_2 are limited to either H or a polymer residue, by defining R_1 and R_2 as including a capping group A that comprises newly recited moieties in addition to the polymers. Claim 10 is objected to for the same reason as claim 9 because of its dependence. Claim 10 is also objected to because it is repetitive. The claim recites four structures. However, three of these, (i), (ii) and (iv), are identical structures comprising in order an oligonucleotide, a linker, a spacer, a polymer residue, a linker, a spacer and an oligonucleotide. While the oligonucleotide portions of the different structures are written as combinations of X_2 and X_3, the structures are identical because the convention in the art is to write oligonucleotides in the 5'-3' orientation, a convention specifically referred to at page 11 of the specification, neither the specification nor the claims defines either X_2 or X_3 as different from this convention.

Claim 21 is objected to because of the following informalities: this claim contains four structures of oligomeric prodrugs. The first and fourth structures are identical. Appropriate correction is required.

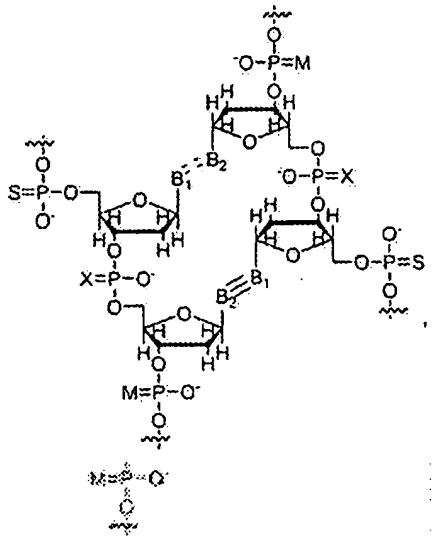
Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 4, 5, 7, 8 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 recites several structures that can be the nucleotide recited in claim 1. This claim is indefinite because some of the structures have positions marked as X but no definition of X is provided. Additionally, the structure shown below apparently shows two strands of nucleotides and it is unknown which nucleotides represent those recited in the claim and it is also unknown if the other nucleotides are also modified with linkers and spacers to be prodrugs.



Additionally, this structure shows that B_1 and B_2 of one strand are connected to B_1 and B_2 of the other strand by either two dashed lines or three solid lines. It is

unknown from this structure if these are meant to represent covalent or non-covalent bonds and what difference is represented by the dashed and solid lines.

Claim 4 recites the limitation "M". There is insufficient antecedent basis for this limitation in the claim.

Claim 5 recites the limitation "oligonucleotide" in line 1. There is insufficient antecedent basis for this limitation in the claim because claim 1 recites only the phrase "oligonucleotide residue".

Claim 7 is indefinite because it states the oligonucleotide residue is RNAi. RNAi is a term recognized in the art as referring to the process of RNA interference. There is no art recognized meaning for an oligonucleotide that is RNAi. The specification does not provide a definition for this term; it appears only in this claim.

Claim 8 recites that in SEQ ID NO: 4 X is "any compatible nucleotide". This phrase is indefinite because there is no art recognized meaning for the term "compatible nucleotide" in the context of the claim and because SEQ ID NO: 4 does not contain any residue X.

Claim 11 is indefinite because it defines a variable Z but no Z appears in the structures shown in the claim. While there is a subscript "z" meant to define the possible number of residues, the definition given for Z does not make sense in this context and the subscript "z" is defined as a numerical value.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claim 1 is directed to oligonucleotides prodrugs comprising an oligonucleotide, at least one spacing group, at least one releasable linking moiety and at least one polymer residue. Claims 2-19 depend from claim 1 and recite limitations regarding the length and identity of the oligonucleotide portion of the prodrug, the L1 and L_4 residues, the polymer residues and the average molecular weight of the polymer.

The claims encompass oligonucleotide prodrugs comprising releasable linker moieties. Claims 11 and 12 recite specific structures of linking moieties that comprise components that are bifunctional spacers. The terms "releasable linker moieties" and "bifunctional spacer" are not explicitly defined in the specification but only exemplified by a list of compounds that identified as being releasable linking moieties or bifunctional spacers. The specification recites at pages 19-25 a list of compounds that are linking moieties and a list of compounds that are bifunctional spacers but neither the specification nor the prior art provide a definition of these terms such that the skilled artisan could envision what structure provides a compound with the function of being a releasable linking moiety or a bifunctional spacer.

In order for the written description provision of 35 USC 112, first paragraph to be satisfied, applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed.

Without a definition of these terms, the skilled artisan would not recognize the structure that provides the function of being a releasable linking moiety or a bifunctional spacer and therefore could not envision the detailed structure of the claimed oligonucleotide prodrugs comprising releasable linking moieties and bifunctional spacers, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 5-19 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Teng et al. (US 6,887,906) in view of Greenwald et al. (US 6,303,569) and Dandliker et al. (US 5,707,813).

The claimed invention is directed to prodrug compounds comprising an oligonucleotide and one or more polymers, linking moieties and spacers. In specific embodiments the oligonucleotide component is a phosphorothioate and may be an antisense, the linking moiety comprises an aromatic group, the antisense sequence is SEQ ID NO: 1 and the polymer component is a polyalkylene oxide such as polyethylene glycol.

Teng et al. teach compositions of antisense oligonucleotides useful for therapeutic purposes. One of these is a sequence 18 bases in length targeted to bcl-2 and designated as SEQ ID NO: 34, which is identical to instant SEQ ID NO: 1. At column 10 Teng et al. teach that the antisense compounds of the invention can comprise modified linkages such as phosphorothioates. At column 17, lines 58-67 Teng et al. teach that the oligonucleotides of their invention can be provided in prodrug form, an inactive form that is converted to active form within a cell. Teng et al. do not explicitly teach the use of polymeric prodrugs.

Greenwald et al. teach that poor solubility and rapid degradation *in vivo* are recognized problems of some therapeutic agents. One solution to these problems is the use of prodrugs; inactive forms of a drug that are metabolized within the body to form

the active agent. The use of prodrugs can allow one to increase the solubility and lifetime of a drug. Greenwald et al. teach polymeric prodrugs illustrated at columns 2-3 as formula I. The prodrugs comprise a polymer region, designated as R_{11}, a linker comprising an aromatic group and a drug component designated as B. At columns 18-19 Greenwald et al. teach that the drug component B includes nucleic acids such as DNA or RNA. At columns 9-10 Greenwald et al. teach that polyalkylene oxides such as polyethylene glycol are a preferred polymer component of the prodrug and that these polymers have molecular weights in the range of 2000-100000. The polymer component can have a capping structure such as an alkyl group or can comprise the structure shown as figure II, which would produce a bis-prodrug, wherein the two drug components are identical or different.

It was well known in the art at the time of invention to employ linkers as a component of an oligonucleotide conjugate. For example Dandliker et al. teach that a commercially available reagent can be used to produce an oligonucleotide having a hexylamine at the 5' terminus. This linker allows the skilled artisan to produce a variety of conjugates by attaching different groups to the oligonucleotide through reaction with the primary amine.

It would have been obvious to one of ordinary skill in the art at the time of invention to produce the bcl-2 sequence of Teng et al. in prodrug form as a polymeric prodrug, including a polymeric bis-prodrug, as taught by Greenwald et al. Teng et al. provide a motivation to make the antisense sequence as a prodrug by explicitly suggesting their oligonucleotides be formulated as prodrugs. Greenwald et al. provide a motivation to make polymeric prodrugs by teaching that polymeric prodrugs allow an

increase in the solubility and stability of therapeutic agents and explicitly suggest their use with nucleic acid drugs. It is further obvious to use hexylamine linkers as a component of the prodrug because Dandliker et al. teach that the person of ordinary skill in the art would be familiar with the use of such linkers due to the commercial availability of reagents that make such linkers and the extensive use of hexylamine linkers for producing a variety of oligonucleotide conjugates. One of ordinary skill in the art would have had a reasonable expectation of success in producing a polymeric prodrug of the bcl-2 sequence because Greenwald et al. provide detailed guidance for the synthesis of polymeric prodrugs.

Thus, the invention of claims 1-3, 5-8, 11-19 and 21 would have been obvious, as a whole, at the time of invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The central FAX Number is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight

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Tracy Vivlemore
Examiner
Art Unit 1635

TV
July 18, 2006

JAMES SCHULTZ, PH.D.
PRIMARY EXAMINER